MINUTES
HUMAN SUBJECTS RESEARCH ADVISORY COMMITTEE
Friday, September 14, 2007
CRC Medical Board Room
3:00 p.m.

Present

Dr. Michael Gottesman, Chair
Dr. Howard Austin,NIDDK/NIAMS
Dr. John Gallin, CRC
Dr. Gilman Grave, NICHD
Dr. Stephen Heishman, for Dr.Karp NIDA
Dr. Sara Hull, for Dr. Candotti, NHGRI
Dr. John Janik, for Dr. Hazra, NCI
Dr. Marian Johnson-Thompson, NIEHS
Dr. Sarah Kindrick, for Ms. Lisa Coronado, RSC
Dr. Sarah Kobrin for Dr. Hatch, NCI/SS
Dr. Jerry Menikoff, Exec. Sec.
Dr. Susan Olivo-Marsten, FELCOM Representative
Dr. Maryland Pao, for Dr. Karp, Combined Neurosciences IRB
Dr. Koneti Rao, NIAID
Dr. Robert Shamburek, NBLBI
Mr.Craig Wladyka, Protocol Administration Representative
Dr. Richard Wyatt, OIR

Absent

Dr. Fabio Candotti, NHGRI
Dr. Christine Grady, CRC/DCB
Dr. Maureen Hatch, NCI SS
Dr. Rohan Hazra, NCI
Dr. Barbara Karp, Combined Neurosciences and NIDA
Dr. Mitchell Max, NIDCR

Guests

Ms. Elaine Ayres, CRC
Ms. Marguerite Bevans, CC/Nursing
Ms. Marianna Bledsoe, OSP
Ms. Valerie Bonham, OGC
Ms. Melissa Bryant, NHLBI
Ms. Laura Cearnal, CC
Ms. Doreen Chaitt, NIAID
Michael Chapple, NEI
Dennis Dixon, NIAID
Ms. Marjorie Gillespie, NINDS
Mr. Peter Glasz, NIDCR
Ms. Anne Gupman, NIDA
Ms. Mary Hall, CC/NHLBI
Ms. Charlotte Holden, OHSR
Ms. Kim Jarema, CC/OPS
Ms. Jane Lambert, NIEHS
Ms. Cathy Little, NIAAA
Ms. Jennifer Morris, NINDS
Mr. Alex Noury, NINDS
Dr. Joan Packenham, NIEHS
Ms. Jeanne Radcliffe, NIMH
Ms. Erin Ramos, NHGRI
Dr. Laura Rodriguez, NHGRI
Dr. Julia Slutsman
Mrs. Janet Smith, OHSR (Ret.)
Ms. Nanette Suksta, NIDCD
Ms. Patricia Sweet, NHLBI
Ms. Darlene Switalski, NIEHS
Ms. Glynnis Vance, NIDDK
Dr. Alison Wichman, NINDS/OCD
Ms. Victoria Willits, NHGRI
Ms. Marcia Wright, OHSR

1. Minutes of the May 11, 2007 meeting. The minutes were approved.

2. "Points to Consider" document for GWAS. Dr. Gottesman reminded the group of the GWAS presentations made at the last HSRAC meeting and discussions about the kind of data being used, whether appropriate informed consent has been/is being obtained, how it is decided whether requests from the database are legitimate, etc.

Ms. Holden said that since the last HSRAC meeting, the GWAS policy has been published in the Federal Register. One important component of this policy is that IRBs at institutions submitting data to the NIH database for GWAS must review the consent documents of the sources of the data to make sure that the study participants were (or will be) appropriately informed about how their samples will be used.

Dr. Rodriguez, special assistant to Dr. Francis Collins, NHGRI, then gave an overview of the guiding principles of GWAS. GWAS facilitates the sharing of large datasets containing coded, de-identified genotypic and phenotypic data obtained in NIH supported or conducted research. The maximum public benefit will be obtained from GWAS studies if as many investigators as possible participate in contributing and using the data. NIH has therefore taken the lead in organizing a national database for GWAS studies, the database of Genotypes and Phenotypes (dbGaP), managed by the National Center for Biotechnology Information (NCBI) of the National Library of Medicine (NLM).

In order to protect the confidentiality of the data and the and privacy of the participants, GWAS policy will require certification from institutional officials that the terms of GWAS policy have been met. In addition, IRBs will be required to verify that the submission and subsequent sharing of data are consistent with the informed consent of study participants and that investigators' plans for de-identifying datasets are consistent with the standards outlined in the policy. The criteria for de-identification are that the identities of data subjects cannot be readily ascertained or otherwise associated with the data by the repository staff or secondary data users, and the 18 identifiers described in the HIPAA Privacy Rule are removed. Before submitting data to GWAS, investigators will be required to submit a random, unique code to the de-identified data. Furthermore, the submitting institution must certify that the identities of research participants will not be disclosed to the NIH GWAS data repository. Similar protections are in place for investigators and institutions seeking data from the NIH GWAS data repository (secondary users).

The NIH has established policies and data use committees (some are already in place) for oversight of the NIH GWAS data repository and for monitoring GWAS data use practices. There will be no public access to individual data, only to ranges of data. Secondary users, who are not engaging in human subjects research (per OHRP), will be identified in order to facilitate collaborations.

There will be a period of exclusivity for publication for a maximum of twelve months for submitting investigators. Any publications by secondary investigators must acknowledge the originating investigators and their institutions.

The GWAS policy was released at the end of August. The Points to Consider document will be released in November. January 25, 2008 is the expected implementation date for the policy.

Dr. Gottesman said that although the issue is complex, work is being done on a simple policy to enable NIH intramural investigators to submit and access data. NIH IRBs and Institutes will play a critical role in data submission and it will be the IRBs' responsibility to review and verify that submitted data are consistent with the informed consent of the original participants, and are in conformance with 45 CFR 46. It should be noted that use of the de-identified information in the database is not considered human subjects research by OHRP.

Ms. Bledsoe reviewed the confidential draft of the "Points to Consider" document, *Points to Consider for IRBs and Institutions in their Review of Data Submission Plans Under NIH's Policy for Sharing of Data Obtained in NIH Supported or Conducted Genome-Wide Association Studies GWAS*. This document was attached to the agenda and has had input from the Office of Science Policy, OHSR, the CC Division of Clinical Bioethics, and other NIH staff. It contains detailed information about NIH's GWAS policy, discussion of the benefits and risks involved in submitting and sharing GWAS data through a central repository, and the safeguards that will be in place at NIH to protect the data. The document also contains specific points for institutions and IRBs to consider in their review and certification of the investigator's plans for data submission, review of consents, de-identification of samples, etc. It is possible that new consents may have to be developed to enable data to be sent to the repository or subjects may have to be re-consented. The document also addresses the risks, in spite of the safeguards in place, of possible identification of samples through the GWAS database, including inadvertent or inappropriate use or disclosure of individually identifiable information, the risk associated with FOIA requests, law enforcement access, etc. The document is not meant to be prescriptive or all-encompassing and NIH recognizes that the complexities of this evolving policy may require additional guidance, which will be issued as needed on the GWAS website at http://grants.nih.gov/grants/gwas/index.htm.

The authors of the document would like to have the Points to Consider document vetted for usefulness by HSRAC members. Specific input is requested on the following questions:

> Is the document helpful?
> Are there areas of the document that are unclear or need further explanation?
> Is the document balanced in the discussion of risks and benefits?
> Are there additional issues that need to be addressed?
> Is additional guidance needed to assist IRBs in their review of data submission plans and informed consent documents?
> Are there major questions or issues related to the content of the document?

Dr. Rao commented that in the case of submission of data from retrospective studies, which may be quite old, the consent language is likely not to be adequate, and it may not be practical to re-consent subjects. He was informed that in the absence of re-consent, data could not be submitted to the GWAS repository although Ms. Bledsoe said that in the case of retrospective data, approval could be sought at the institutional level to use the data, even if the consents were not up to the current standard. However, Dr. Menikoff added that because of the special rules under which GWAS operates, the submission of data must be consistent with the consents. Dr. Gottesman later suggested that instead of re-consenting subjects, one possibility for IRBs to consider could be informing subjects by letter of the intention to send their data to the GWAS repository, which would not be done if they objected.

Dr. Austin was informed that under GWAS policy, there is no provision for an IRB to waive consent in the case of retrospective studies. If an IRB concludes that the original consent is not consistent with GWAS use, then the data should not be submitted to the repository.

Dr. Gallin thought the policy sets too rigid a precedent because the de-identification criteria (removal of the 18 HIPAA identification elements -- page 7 of the document) are too restrictive. As a result, the power of the data will be diminished. He believes release of zip codes (important in demographic research) or subjects' photographs, for instance, should be permitted if the subjects are willing. Ms. Bonham pointed out that NIH is not subject to HIPAA regulations, but Ms. Bledsoe countered that the institutes as users of the database are. It was pointed out that investigators can go back to the original data *via* the originating principal investigator to set up IRB-reviewed and -approved collaborations if more information is sought.

Dr. Gottesman agreed that the information in the GWAS database may be less than perfect medically, but will be very useful for investigators looking at genes. He reminded HSRAC that law enforcement agencies can gain access to databases such as dbGaP. Ms. Rodriguez said that certificates of confidentiality are highly recommended for prospective studies, but it would be too late to obtain them for existing samples being sent to the database. dbGaP itself is not eligible for a certificate of confidentiality because it contains only de-identified information.

Dr. Austin said it would be helpful if there were more explicit information about what is wanted in consent documents for data being sent to the GWAS database, i.e., what are the mandatory and optional elements. Currently, typical consent documents where it is expected samples will be stored for future use and/or genetic studies may be quite comprehensive in their language, but do not state that that data will be sent to a government-controlled repository.

Ms. Bledsoe said she recognizes the need for additional guidance for IRBs, and OSP is looking at the policies and consent forms developed for GAIN studies reviewed by the NHGRI IRB, to identify core principles and to develop model consent language (but not a model consent document). (GAIN is a public-private partnership between NIH, The

Foundation for NIH, industry and others to encourage whole genome association studies of common diseases.) Dr. Menikoff noted that the information about data sharing and analysis in the GAIN consent documents is vague, e.g., they do not mention "a genome-wide analysis", and yet those consents have been found to be acceptable for submitting data to dbGaP. Ms. Rodriguez said that NHGRI is trying to capitalize on its experiences with six GAIN studies so far, in a phased approach. The timeline for the GWAS policy lends urgency to this effort.

3. GWAS Data not Subject to new NIH GWAS Policy. Dr. Gottesman said that data is already coming in to dbGaP before the January 25 implementation date for GWAS policy. It is important that these data not be treated differently from post-January 25 data, particularly as NCBI is an intramural component for which Dr. Gottesman is responsible.

Dr. Menikoff suggested that a slightly less formal policy be allowed for these studies but pointed out that a mechanism has to be put in place for additional review of the consents. OHSR could fulfill this role, or the consents could be sent to an IRB (an IRB at NIH, or the one that originally approved the study) for additional review. Ms. Bonham suggested that exemptions could be sought from OHSR for coded information.

4. Scope of NIH Employees Being Engaged in Research. Dr. Menikoff said that the NIH FWA applies to both intramural and extramural NIH employees. Extramural employees may be engaged in research in the course of their duties, and if so, would come under Dr. Gottesman's authority as the responsible NIH official for the FWA. It is important to find out the numbers of extramural employees in this category and to make sure they receive computer-based training in human subjects research. The number of such employees could be minimized by ensuring they use coded data, or that their research is overseen by an intramural IRB or a reliance on an extramural IRB.

Dr. Menikoff also noted that intramural employees doing research elsewhere in the USA or overseas are still subject to NIH oversight under the FWA. Work done elsewhere requires review here at NIH unless it is covered by an OHSR- negotiated reliance on a non-NIH IRB. This does not apply to NIH employees performing clinical care only.

5. DSMB Review of Studies where NIH has Patent Interest Dr. Gottesman noted that NIH does not preclude intramural investigators who participate in clinical trials from receiving interest on royalties, although some academic centers do not allow this. NIH IRBs must be aware of any investigators' royalty interests and must ensure that there is a DSMB-like committee to oversee their activities. Recently, it came to Dr. Gottesman's attention that one DSMB did not know why it was being asked to evaluate an investigator's activities and did not think this role was appropriate for a DSMB. Dr. Gottesman said that is important to protect investigators by having someone neutral and independent to review their studies. NIAID has two such studies overseen by a DSMB-like committee and NCI has numerous studies monitored by a four-person special committee, which includes an outside statistician and an ethicist. It was suggested that "external monitor" would be a more appropriate term than "DSMB-like committee."

Dr. Hull said that an IRB reviewing a recent study asked for an ethics consultation to make sure each subject knew the extent of the investigator's financial stake. It was not clear exactly how to fulfill the IRB's requirement.

6. AAHRPP Accreditation. Dr. Gottesman reminded the group that the NIH human subjects protection program is not accredited, although it participated in AAHRPP's pilot accreditation exercise done at NIH in December/January 200l/2002. Since then, AAHRPP has developed its requirements and has formally accredited other organizations. It is in NIH's best interests to become accredited, but the process will require time and energy.

Dr. Menikoff presented the requirements for accreditation. These involve completing an application form; submitting an intense self assessment of NIH's human research protection program, using the AAHRPP evaluation form and including supporting documents; an on-site evaluation, and AAHRPP Council Review. The application form has seven parts, five domains and 20 standards.

The on-site evaluation occurs within a few months after the application is submitted. Thirty days after the site visit and review by the AAHRPP Council, AAHRPP sends a draft site visit report to the institutions for comment. A response to the draft site visit report, which is an integral part of the application, is due within 30 days. AAHRPP grants Full Accreditation, Qualified Accreditation or Accreditation Pending or Accreditation withheld status to the applicant organization. It charges an application fee and a yearly fee for maintaining accreditation. Fees are based on the size and complexity of the organization. Renewal of accreditation is required every three years.

Dr. Menikoff said it is clear that in terms of the AAHRPP requirements, NIH has significant gaps in its written policies and procedures, which will have to be addressed during the self-assessment process. The goal for applying to AAHRPP for accreditation is April, 2008, but this may be unrealistic given the nature of the steps that must be completed prior to submitting the application.

Announcement. The next meeting will take place on **November 16** at **4:00 p.m**. (This is a change from the originally scheduled date, November 9.)

The meeting concluded at 5:00 p.m.